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FDA Review Patterns of 'De Novo' Submissions

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Abstract

Following the enactment of the FDA Modernization Act of 1997, FDA established a new regulatory route intended for medical devices that present a lower level of risk than those classified into Class III. The regulatory path is referred to as a 'De Novo' application, and involves two phases – an initial standard 510(k) process, followed by a review of the risk level of the technology – the De Novo review. In FDA's Guidance Document describing the De Novo application, the agency committed to completing the second phase – the De Novo review – within 60 days. An analysis of all 'De Novo' devices cleared by the FDA during the period 1998 – 2009 identified a total of 54 such products. Until 2007 the average duration of the De Novo review phase was 62 days (in line with FDA's commitment) and an overall review duration (including the initial review of the 510(k) application) of 245 days. However, devices cleared since 2007 experienced an average De Novo review period of 240 days, and an average total review time of 482 days. Such a long period significantly exceeds FDA's commitment for the duration of the review process of even most panel-track, pre-market approval (PMA) devices.

Background

Medical device manufacturers interested in marketing their products in the USA are required to secure FDA marketing clearance. The process for securing such a clearance is generally based on the device's risk level: Class I (lowest risk) devices are exempt from applying for approval, Class II devices follow in most cases a regulatory path known by its acronym as the '510(k) process' and Class III devices are generally required to submit a premarket approval (PMA) application. The 510(k) process[2] requires the sponsor to demonstrate that the new (candidate) device is substantially equivalent to a 'predicate device', that was either in interstate commerce before May 28, 1976[3], or had been cleared for marketing using the 510(k) process. Medical products that could not be determined as substantially equivalent to any predicate device(s), had to be automatically classified as Class III and follow the PMA regulatory path, even when their risk level would justify a Class II classification. Class III default classification clearly increased the regulatory and testing burden necessary to secure marketing clearance for such devices.

Section 207 of the FDA Modernization Act of 1997 (FDAMA) created for the first time a new regulatory path, intended to address the regulatory limitations of the 510(k) process for low-risk devices using new technologies. The process is described in a guidance document issued by the Office of Device Evaluation, Center for Devices and Radiological Health, FDA on February 19, 1998[4]. The process is titled "Evaluation of Automatic Class III Designation" (or 'De Novo' application), and is intended to offer the

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[2] Named after the specific statute in the regulation.

[3] The enactment date of the Medical Device Amendments to the Food, Drug and Cosmetics Law

[4] FDA/CDRH/ODE. New Section 513(f)(2) – Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff. February 19, 1998.

manufacturer of a new technology device clearance path under the 510(k) process even when no predicate device exists. Table 1 lists the main steps involved in this process:

Step	Sponsor	FDA	Time Frame	Comments
I	Submit 510(k) for new device			No predicate device exists
II		Review 510(k) and issue NSE[5] letter for no predicate		• No review time specified • Device is automatically designated as Class III
III	Request for Evaluation of Automatic Class III Designation submitted		30 days	
IV		Review and issue order establishing classification	60 days	FDA can either leave Class III designation, or reclassify as Class I or Class II
V		Publish finding in Federal Register	30 days	

Table 1. Evaluation of Automatic Class III Designation ('De Novo') Process

The FDA has therefore mandated three elements in this process that have clear time-frames:

1. The sponsor's request for evaluation of Automatic Class III Designation needs to be received by FDA within 30 days of issuing the NSE letter.
2. The FDA mandated itself to complete its review and announce its decision regarding the sponsor's request within 60 days of receiving the request.
3. The FDA mandated itself to publish its finding in the Federal Register within 30 days following the issue of the classification order.

The goal of this analysis was to evaluate the actual timeframes associated with the different steps of the review process over the 12 years this process has been in effect.

Methodology

FDA has developed an electronic database[6] that allows public access to certain elements of cleared regulatory submissions. A total of 54 records of devices cleared by the 'De Novo' process in the period of August 20, 1999 through September 11, 2009 were identified and analyzed.

The actual dates used for the determination of the review times were based on the information included in the clearance letters published by the FDA (NSE letter issued by the FDA and submission of the De Novo application by the sponsor), and the information included in the 510(k) database for each one of the submissions (submission of the original 510(k) application). The review periods were calculated as:

[5] Not Substantially Equivalent (NSE)

[6] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

- 510(k) Review Time – the elapsed time from the original 510(k) submission date (from the 510(k) database) to the date of the NSE determination (from the clearance letter)
- De Novo Review Time – the elapsed time from the submission of the De Novo application (from the clearance letter) to the date stamp of the clearance letter

Results

The objective of this analysis was to assess whether timelines associated with the De Novo Process are in line with FDA's stated goals. Out of the total number of 54 applications cleared during 1999 - 2009, only 50 had all dates necessary to establish the corresponding individual review periods, while 51 had sufficient information to establish at least one of the review times.

Figure 1 describes the distribution of the 510(k) review time (Step II in Table 1), as a function of the clearance date for each of the applications analyzed (1a), grouped in intervals of 3 years (1b). The average times from the time before 2007 increased from 196 days to 279 days (median 161 vs. 268) since the beginning of 2007. Figure 1 shows a gradual increase of the median initial review time. The differences do not reach statistical significance (U-test, p=0.14, 1998-2000 vs. 2007-2009).

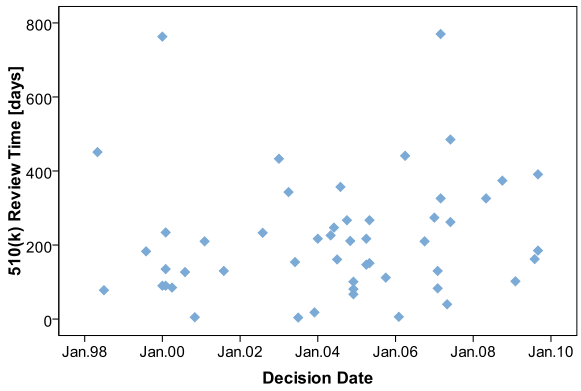

Figure 1a. Review times (days) of the 510(k) phase (Step II in Table 1).

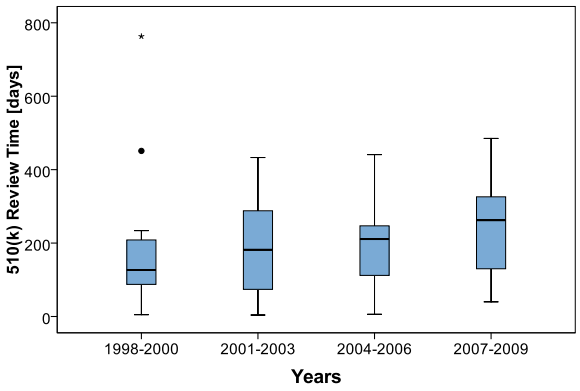

Figure 1b. Review times (days) of the 510(k) phase (Step II in Table 1). Boxplot. Boxes show first to third quartile. Line within box indicates median. Whiskers show high/low. Circles denote outliers, asterisks denote extremes.

Figure 2 describes the distribution of the 'De Novo' phase (Step IV in Table 1 as a function of the clearance date (2a – raw data; 2b – boxplot). An examination of the data demonstrates the recent significant increase in the review periods over the last four years. Until the end of 2006, the review of all but two applications (95% of applications) was completed within 100 days, with an average review time of 62 days (median 51). However, starting in 2007, only four out of 13 (31%) applications were reviewed in less than 100 days, and the average jumped to over 241 days (median 217). This difference is statistically highly significant compared to each previous 3 year intervals (Kruskal-Wallis-test, $p < 0.01$).

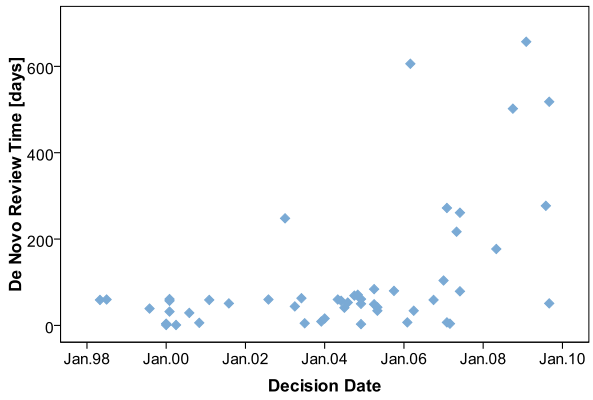

Figure 2a. Review times (days) of the De Novo phase (Step IV in Table 1).

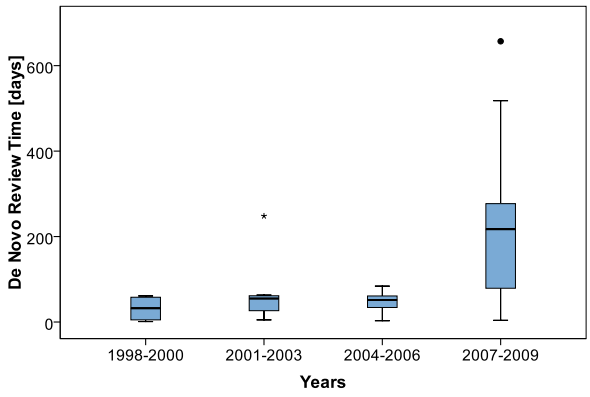

Figure 2b. Review times (days) of the De Novo phase (Step IV in Table 1). Boxplot.

The increase in the duration of the review period of the 'De Novo' phase, had a dramatic effect on the duration of the overall review period (i.e. the sum total of both review periods), as demonstrated in Figure 3 (3a – raw data; 3b – boxplot). Whereas until the end of 2006 – the average overall review time was 245 days (median 220), devices cleared since the beginning of 2007 experienced an average overall review time of 482 days (1.3 years; median 439 days). This difference is also statistically highly significant compared to each previous 3 year intervals (Kruskal-Wallis-test, $p < 0.01$).

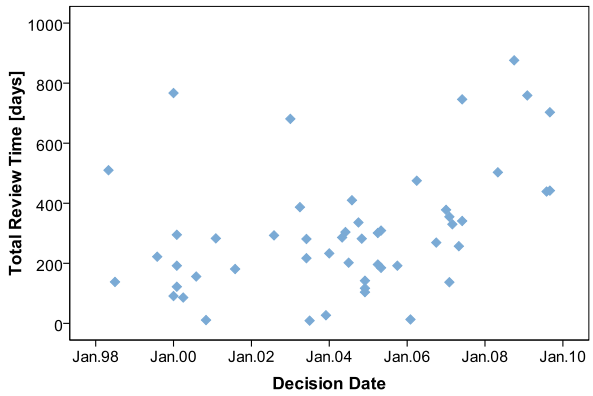

Figure 3a. Duration of total review times of De Novo products (Step II + Step IV in Table 1).

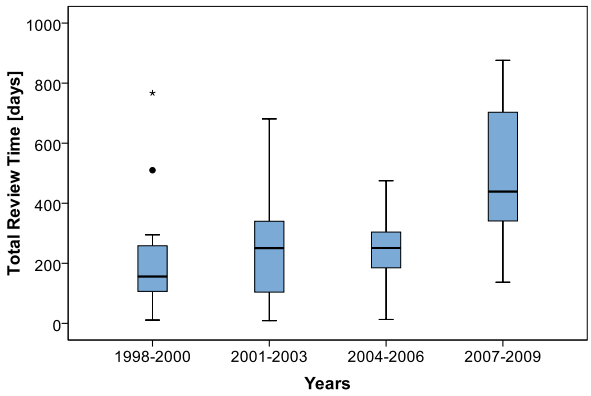

Figure 3b. Duration of total review times of De Novo products (Step II + Step IV in Table 1). Boxplot.

In trying to better understand the pattern of review times we have analyzed the data based on the nature of the device, i.e. whether the device was diagnostic or therapeutic. Of the 54 successful submissions, there were 38 diagnostic devices and 16 therapeutic devices. Table 1 provides a summary of the median and average review times of both the diagnostic and therapeutic devices, detailed for both the 510(k) component and the De Novo component. The median and average review times of the 510(k) phase are similar for both diagnostic and therapeutic devices. However, comparing the review times of the De Novo phase identified a large difference in both the median and average review times: The median review time of therapeutic devices (84 days) is longer than the corresponding value for diagnostic devices (50 days) by > 50%, while the average review time (205 days) is more than three times longer than the corresponding value for diagnostic devices (65 days) (statistically significant, $p<0.01$). These differences carry over to the total review times that are ~50% longer for therapeutic devices than the corresponding values for diagnostic devices.

	510(k) Review [days] [Median / Average]	De Novo Review [days] [Median / Average]	Total Review [days] [Median / Average]
Diagnostic	210 / 226	50 / 65	236 / 283
Therapeutic	211 / 213*	84 / 205**	303 / 410***

Table 2. Review times for diagnostic and therapeutic devices
(* n.s., p = 0.968; ** p < 0.01; *** n.s., p = 0.058; U-test, two-sided)

The review times of the individual review panels are listed in Table 3. Fourteen review panels have processed De-Novo submissions, with five panels clearing 60% of all devices (32/54). Three panels – Immunology, Microbiology and Clinical Chemistry cleared 22 immunological and/or genetic tests, representing the majority of diagnostic devices (22/38), and ~40% of all De-Novo submissions (22/54). Submissions cleared in under one month included only diagnostic products such as a test for West Nile Virus – cleared in 9 days, test for Triage B-Type Natriuretic Peptide – cleared in 11 days and a test for Influenza Virus – cleared in 13 days.

Review Specialty	Number of Submissions	Median 510k Review Time [Days]	Average 510k Review Time [Days]	Median De Novo Review Time [Days]	Average De Novo Review Time [Days]	Median Total Review Time [Days]	Average Total Review Time [Days]	Shortest Total Review Time [Days]	Longest Total Review Time [Days]	Range [Days]
Immunology	9	151	216	42	41	196	257	137	475	338
Microbiology	7	226	186	60	56	286	243	9	503	494
Clinical Chemistry	6	148	166	24	27	197	193	11	410	399
Gastroenterology/Urology	5	210	306	45	41	249	338	181	770	589
General/Plastic Surgery	5	162	156	277	356	439	512	304	759	455
OB/GYN	4	243	251	88	106	330	357	86	681	595
Cardiology	3	101	101	56	56	192	198	122	281	159
Dental	3	217	176	61	68	295	245	138	301	163
General Hospital	3	267	264	217	182	336	446	257	746	489
Ear Nose Throat	2	233	233	333	333	450	450	293	606	313
Hematology	2	118	118	13	13	130	130	27	233	206
Neurology	2	413	413	281	281	693	693	510	876	366
Toxicology	2	205	205	47	47	252	252	117	387	270
Anesthesiology	1	763	763	4	4	767	767	767	767	0

Table 3. Distribution of review times for different review panels

Discussion and Conclusions

The De Novo regulatory route was developed by FDA in order to offer a path to the market for medical devices that present a lower level of risk than products required to follow the PMA process, while not qualifying for the traditional 510(k) process due to the lack of a predicate (i.e. similar) technology. A two-phase process, requiring first a complete 510(k) review, evaluating the technical, pre-clinical and clinical information, followed by a well-structured review of the risk level of the new device, was developed by the FDA, with a commitment to complete the second review phase within 60 days. A review of all De Novo submissions cleared by the end of 2009 and published on FDA's web-site by April, 2010 identified 54 such devices[7]. The 510(k), De Novo and total review times were analyzed for all submissions.

The study of review times revealed that even though 14 different review panels were able to process De Novo submissions, most of the panels (8/14) processed 1 – 3 submissions each, making it difficult to identify patterns. Three review panels (Immunology, Microbiology and Clinical Chemistry) processed a total of 22 submissions, all involving diagnostic blood tests. Diagnostic products had in general shorter review times compared to therapeutic devices. It appears that tests that have a significant impact on public health were cleared within days (e.g. West Nile and Influenza Virus tests were cleared within 9 and 13 days correspondingly).

The review process seemed to function well during the first nine years of the program's existence, as FDA was able to generally follow its self-imposed 60-days time limit for the classification of devices that embarked on the De Novo regulatory route, and a resulting overall average review time of eight months. However, starting in 2007 review times have extended, leading to an average review time of eight months for the De Novo phase alone, and a total average review time of 16 months.

It appears that since the beginning of 2007, the agency has not been able to meet its self-established deadlines for classification and clearance of devices that are placed in the 'De Novo' group of submissions. This has led to a troubling extension of the regulatory review process, far beyond FDA's commitments under the reauthorization of the MDUFA (Medical Device User Fee Amendments) of 2007[8] to review 90% of all PMA-related panel-track submissions within 295 days, and 98% of 510(k) submissions within 150 days. The review times of De Novo products during the last four years have been constantly increasing and are now almost twice as long as FDA's promised review times of panel-track PMA submissions, and more than three-times longer than the committed review time of 510(k) submissions. With the emergence of new medical technologies, sponsors have been encouraged to make greater use of the De Novo regulatory route. The results presented in this paper suggest, that unless the program is revamped, sponsors selecting the De Novo route should expect much longer review times than the traditional 510(k) or even PMA paths.

[7] The database lists 55 devices, however, one device was found to be substantially equivalent to a predicate, even though it is listed in the De Novo group.

[8] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/UCM109102.pdf